

**IN THE CLAIMS:**

Kindly amend the claims as follows:

1                   1.     (Currently Amended)     A method of detecting a  
2 malignant tumor in a human subject, comprising:

3                   (a)     collecting a sample of a bodily substance containing human  
4 nucleic acid or protein, said nucleic acid or protein having  
5 originated from cells of the human subject;

6                   (b)     detecting quantitatively or semi-quantitatively in the sample  
7 a level of expression for laminin  $\alpha$ 4 subunit protein or  
8 *laminin  $\alpha$ 4-specific mRNA* complementary to a nucleic acid  
9 of SEQ ID NO:1; and

10                  (c)     comparing the expression level in (b) to a level of  
11 expression in a normal control, wherein overexpression of  
12 laminin  $\alpha$ 4 subunit protein or laminin  $\alpha$ 4-specific mRNA,  
13 with respect to the control, indicates the presence of a  
14 malignant tumor in the human subject.

1                   2.     (Previously Presented)     The method of Claim 1, wherein  
2 the bodily substance is blood, urine, lymph, cerebro-spinal fluid, skin, stroma,  
3 vascular epithelium, oral epithelium, vaginal epithelium, cervical epithelium,  
4 uterine epithelium, intestinal epithelium, bronchial epithelium, esophageal  
5 epithelium, or mesothelium.

1                   3.     (Previously Presented)     The method of Claim 1, wherein  
2 the bodily substance is a tissue sample.

1                   4.     (Original)     The method of Claim 3, wherein the tissue  
2     sample is collected from the brain of the subject.

1                   5.     (Original)     The method of Claim 3, wherein the tissue  
2     sample is a tumor tissue.

1                   6.     (Original)     The method of Claim 1, wherein the bodily  
2     substance is plasma.

1                   7.     (Original)     The method of Claim 1, wherein the bodily  
2     substance is a cellular material.

1                   8.     (Original)     The method of Claim 7, wherein the cellular  
2     material is derived from the human subject's brain kidney, bladder, ureter,  
3     urethra, thyroid, parotid gland, submaxillary gland, sublingual gland, lymph  
4     node, bone, cartilage, lung, mediastinum, breast, uterus, ovary, testis,  
5     prostate, cervix uteri, endometrium, pancreas, liver, spleen, adrenal,  
6     esophagus, stomach, or intestine.

1                   9.     (Previously Presented)     The method of Claim 7, wherein  
2     the cellular material is a carcinoma, sarcoma, lymphoma, mesothelioma,  
3     melanoma, glioma, nephroblastoma, glioblastoma, oligodendroglioma,  
4     astrocytoma, ependymoma, primitive neuroectodermal tumor, atypical  
5     meningioma, malignant meningioma, or neuroblastoma.

1                   10. (Previously Presented) The method of Claim 8, wherein  
2 the cellular material is a hyperplastic and/or cytologically dysplastic cellular  
3 growth or proliferation that is benign prostatic hyperplasia/dysplasia or cervical  
4 hyperplasia/dysplasia.

11-12 (Cancelled)

1                   13. (Previously Presented) The method of Claim 2, wherein  
2 the expression level of *laminin*  $\alpha$ 4-specific mRNA is detected by measuring  
3 RNA.

1                   14. (Currently Amended)     The method of Claim 2, wherein  
2 the expression level of *laminin*  $\alpha 4$ -specific mRNA is detected by measuring  
3 cDNA.

1                   15. (Previously Presented)     The method of Claim 2, wherein a  
2 gene expression microarray is used to detect the level of expression of *laminin*  
3  $\alpha 4$ -specific mRNA.

1                   16. (Previously Presented)     The method of Claim 1, further  
2 comprising detecting the overexpression of laminin  $\beta 1$  subunit protein or  
3 *laminin*  $\beta 1$ -specific mRNA relative to the normal control.

1                   17. (Original Claim)     The method of Claim 1, further  
2 comprising detecting quantitatively or semi-quantitatively in the sample a level  
3 of expression with respect to a normal control, of a gene encoding a protein  
4 selected from the group consisting of insulin-like growth factor binding protein  
5 precursor 3, transforming growth factor- $\beta$ -induced gene, vascular endothelial  
6 growth factor, connective tissue growth factor, human insulin-like growth  
7 factor binding protein precursor 5, placental growth factor, transcription factor  
8 Ap-2, human insulin-like growth factor II, epidermal growth factor receptor,  
9 matrix metalloproteinase-2, keratin 18, vimentin, fibronectin 1, phospholipase  
10 A2 receptor, desmoplakin, tropomodulin, tenascin C, and collagen type IV  $\alpha 1$   
11 chain, or detecting a combination of expression levels for any of these.

1                   18. (Currently Amended)     A method of diagnosing the  
2 presence of a glioma in a human subject, comprising:

3                   (a) obtaining a sample from the brain of the human subject;

4                   (b) detecting quantitatively or semi-quantitatively in the sample  
5 a level of expression for laminin  $\alpha$ 4 subunit protein or  
6 *laminin  $\alpha$ 4-specific mRNA* complementary to a nucleic acid  
7 of SEQ ID NO:1; and

8                   (c) comparing the expression level in (b) to a level of  
9 expression in a normal control, wherein overexpression of  
10 laminin  $\alpha$ 4 subunit protein or *laminin  $\alpha$ 4-specific mRNA*,  
11 with respect to the control, indicates the presence of  
12 glioma in the subject.

19-20 (Cancelled).

1                   21. (Previously Presented)     The method of Claim 18, wherein  
2 the expression level of *laminin  $\alpha$ 4-specific mRNA* is detected by measuring  
3 RNA.

1                   22.   (Previously Presented)   The method of Claim 18, wherein  
2   the expression level of *laminin*  $\alpha 4$ -specific mRNA is detected by measuring  
3   cDNA.

1                   23.   (Previously Presented)   The method of Claim 18 wherein  
2   a gene expression microarray is used to detect the level of expression of  
3   *laminin*  $\alpha 4$ -specific mRNA.

1                   24.   (Previously Presented)   The method of Claim 18, further  
2   comprising detecting the overexpression of laminin  $\beta 1$  subunit protein or  
3   *laminin*  $\beta 1$ -specific mRNA relative to the normal control.

1                   25.   (Original Claim)   The method of Claim 18, further  
2   comprising detecting quantitatively or semi-quantitatively in the sample a level  
3   of expression with respect to a normal control, of a gene encoding a protein  
4   selected from the group consisting of insulin-like growth factor binding protein  
5   precursor 3, transforming growth factor- $\beta$ -induced gene, vascular endothelial  
6   growth factor, connective tissue growth factor, human insulin-like growth  
7   factor binding protein precursor 5, placental growth factor, transcription factor  
8   Ap-2, human insulin-like growth factor II, epidermal growth factor receptor,  
9   matrix metalloproteinase-2, keratin 18, vimentin, fibronectin 1, phospholipase  
10   A2 receptor, desmoplakin, tropomodulin, tenascin C, and collagen type IV  $\alpha 1$   
11   chain, or detecting a combination of expression levels for any of these.

1                   26.   (Original Claim)   The method of Claim 18, wherein the  
2   sample is a tumor tissue.

1                   27. (Original Claim) The method of Claim 18, wherein the sample  
2 comprises plasma.

1                   28. (Currently Amended) A method of predicting the  
2 recurrence of a malignant tumor in a human subject from whom a tumor has  
3 been resected, comprising:  
4                   (a) obtaining a tissue sample from the human subject, said tissue  
5 sample being from a region adjacent to the site of the  
6 tumor;  
7                   (b) detecting quantitatively or semi-quantitatively a level of  
8 expression for laminin  $\alpha 4$  subunit protein or *laminin  $\alpha 4$ -*  
9 *specific* mRNA complementary to a nucleic acid of SEQ ID  
10 NO:1 in the sample; and  
11                   (c) comparing the expression level in (b) to a level of expression in  
12 a normal tissue control, wherein overexpression of laminin  
13  $\alpha 4$  subunit protein or *laminin  $\alpha 4$ -specific* mRNA, with  
14 respect to the control, is predictive of a recurrence of a  
15 malignant tumor in the subject.

1                   29. (Original Claim) The method of Claim 28, wherein the  
2 tissue sample is histopathologically normal in appearance.

30 -31 (Cancelled).

1                   32. (Previously Presented) The method of Claim 28, wherein  
2 the expression level of *laminin  $\alpha 4$ -specific* mRNA is detected by measuring  
3 RNA.

1           33. (Previously Presented) The method of Claim 28, wherein  
2 the expression level of *laminin*  $\alpha 4$ -specific mRNA is detected by measuring  
3 cDNA.

1           34. (Previously Presented) The method of Claim 28, wherein  
2 a gene expression microarray is used to detect the level of expression of  
3 *laminin*  $\alpha 4$ -specific mRNA.

1           35. (Original Claim) The method of Claim 28, further  
2 comprising detecting quantitatively or semi-quantitatively in the sample a level  
3 of expression with respect to a normal tissue control, of a gene encoding a  
4 protein selected from the group consisting of insulin-like growth factor binding  
5 protein precursor 3, transforming growth factor- $\beta$ -induced gene, vascular  
6 endothelial growth factor, connective tissue growth factor, human insulin-like  
7 growth factor binding protein precursor 5, placental growth factor,  
8 transcription factor Ap-2, human insulin-like growth factor II, epidermal growth  
9 factor receptor, matrix metalloproteinase-2, keratin 18, vimentin, fibronectin 1,  
10 phospholipase A2 receptor, desmoplakin, tropomodulin, tenascin C, and  
11 collagen type IV  $\alpha 1$  chain, or detecting a combination of expression levels for  
12 any of these.

1           36. (Previously Presented) The method of Claim 28, further  
2 comprising detecting the overexpression of laminin  $\beta 1$  subunit protein or  
3 *laminin*  $\beta 1$ -specific mRNA relative to the normal tissue control.

37-43 (Cancelled).



1                   44. (Currently Amended)     A method of predicting the  
2 recurrence of a glioma in a human subject from whom a glioma has been  
3 resected, comprising:

4                   (a) obtaining a tissue sample from the brain of the human  
5 subject, said tissue sample being from a region adjacent to  
6 the site of the glioma;

7                   (b) detecting quantitatively or semi-quantitatively a level of  
8 expression for laminin  $\alpha 4$  subunit protein or *laminin  $\alpha 4$ -*  
9 *specific mRNA* complementary to a nucleic acid of SEQ ID  
10 NO:1 in the sample; and

11                   (c) comparing the expression level in (b) to a level of expression in  
12 a normal tissue control, wherein overexpression of laminin  
13  $\alpha 4$  subunit protein or *laminin  $\alpha 4$ -specific mRNA*, with  
14 respect to the control, is predictive of a recurrence of  
15 glioma in the subject.

1                   45. (Original Claim)     The method of Claim 44, wherein the  
2 tissue sample is histopathologically normal in appearance.

46-47 (Cancelled).

1                   48. (Previously Presented)     The method of Claim 44, wherein  
2 the expression level of *laminin  $\alpha 4$ -specific mRNA* is detected by measuring  
3 RNA.

1                   49.   (Previously Presented)   The method of Claim 44, wherein  
2   the expression level of *laminin*  $\alpha$ 4-specific mRNA is detected by measuring  
3   cDNA.

1                   50.   (Previously Presented)   The method of Claim 44, wherein  
2   a gene expression microarray is used to detect the level of expression of  
3   *laminin*  $\alpha$ 4-specific mRNA.

1                   51.   (Original Claim)   The method of Claim 44, further  
2   comprising detecting quantitatively or semi-quantitatively in the sample a level  
3   of expression with respect to a normal tissue control, of a gene encoding a  
4   protein selected from the group consisting of insulin-like growth factor binding  
5   protein precursor 3, transforming growth factor- $\beta$ -induced gene, vascular  
6   endothelial growth factor, connective tissue growth factor, human insulin-like  
7   growth factor binding protein precursor 5, placental growth factor,  
8   transcription factor Ap-2, human insulin-like growth factor II, epidermal growth  
9   factor receptor, matrix metalloproteinase-2, keratin 18, vimentin, fibronectin 1,  
10   phospholipase A2 receptor, desmoplakin, tropomodulin, tenascin C, and  
11   collagen type IV  $\alpha$ 1 chain, or detecting a combination of expression levels for  
12   any of these.

1                   52.   (Previously Presented)   The method of Claim 44, further  
2   comprising detecting the overexpression of laminin  $\beta$ 1 subunit protein or  
3   *laminin*  $\beta$ 1-specific mRNA relative to the normal tissue control.

53-59 (Cancelled).

1                   60. (Currently Amended)       A method of ranking a malignant  
2 tumor in a human subject, wherein said ranking orders the tumors in terms of  
3 ~~invasiveness and aggressiveness, comprising:~~

4                   (a) obtaining a tissue sample from the human subject, said  
5 sample comprising a cell expressing a plurality of mRNA  
6 species that are detectably distinct from one another;

7                   (b) detecting quantitatively or semi-quantitatively an expression  
8 level ~~for at least two of the plurality of mRNA species,~~  
9 ~~wherein at least one of the detected mRNA species is a of~~  
10 laminin  $\alpha$ 4 subunit protein or laminin  $\alpha$ 4-specific mRNA  
11 complementary to a nucleic acid of SEQ ID NO:1 and at  
12 ~~least one is specific to a growth factor-related gene or to a~~  
13 ~~structural gene other than a laminin gene;~~

14                  (c) constructing an expression profile of the sample comprising  
15 a combination of the detected expression levels of *laminin*  
16  *$\alpha$ 4*-specific mRNA and ~~the at least one other mRNA species~~  
17 ~~specific to the growth factor-related gene or to the~~  
18 ~~structural gene other than a laminin gene; and~~

19                  (d) comparing the expression profile in (c) to an expression  
20 profile for a normal tissue control, wherein a level of  
21 overexpression of *laminin  $\alpha$ 4*-specific mRNA, with respect  
22 to the control, is indicative of the presence of and degree  
23 of invasiveness of the tumor in the subject, ~~wherein a level~~  
24 ~~of overexpression of the structural gene other than a~~  
25 ~~laminin gene, with respect to the control, is indicative of~~  
26 ~~degree of tumor invasiveness, and wherein a level of~~  
27 ~~overexpression of the growth factor-related gene, with~~  
28 ~~respect to the control, is indicative of degree of tumor~~

29                                   aggressiveness.

30

1                   61. (Currently Amended)     The method of Claim 60, further  
2 comprising a step of detecting an expression level of and a step of comparing  
3 said expression level of at least one growth factor-related gene or a structural  
4 gene other than a laminin gene or products of said genes wherein the growth  
5 factor-related gene encodes a protein selected from the group consisting of  
6 insulin-like growth factor binding protein precursor 3, transforming growth  
7 factor- $\beta$ -induced gene, vascular endothelial growth factor, connective tissue  
8 growth factor, human insulin-like growth factor binding protein precursor 5,  
9 placental growth factor, transcription factor Ap-2, human insulin-like growth  
10 factor II, and epidermal growth factor receptor.

1                   62. (Currently Amended)     The method of Claim ~~60~~ 61,  
2 wherein the structural gene encodes a protein selected from the group  
3 consisting of matrix metalloproteinase-2, keratin 18, vimentin, fibronectin 1,  
4 phospholipase A2 receptor, desmoplakin, tropomodulin, tenascin C, and  
5 collagen type IV  $\alpha$ 1 chain.

1                   63. (Original Claim)     The method of Claim 60, wherein the  
2 expression level of *laminin  $\alpha$ 4*-specific mRNA is detected by measuring RNA.

1                   64. (Original Claim)     The method of Claim 60, wherein the  
2 expression level of *laminin  $\alpha$ 4*-specific mRNA is detected by measuring cDNA.

1                   65. (Original Claim)    The method of Claim 60, wherein a  
2 gene expression microarray is used to detect the level of expression of *laminin*  
3  $\alpha 4$ -specific mRNA.

1                   66. (Original Claim)    The method of Claim 60, further  
2 comprising detecting the overexpression of *laminin*  $\beta 1$ -specific mRNA relative  
3 to the normal tissue control.

1                   67. (Original Claim)    The method of Claim 60, wherein the  
2 tissue sample is brain tissue.

1                   68. (Original Claim)    The method of Claim 60, wherein the  
2 tumor is a glial tumor.

69-74           (Cancelled).

1                   75. (Previously Presented)   The new method of Claim 1,  
2 further comprising detecting the overexpression of a gene encoding laminin  $\beta 1$   
3 subunit relative to the normal control.

1                    76.    (Previously Presented)    The method of Claim 18, further  
2   comprising detecting the overexpression of a gene encoding laminin  $\beta$ 1 subunit  
3   relative to the normal control.

1                    77.    (Previously Presented)    The method of Claim 28, further  
2   comprising detecting the overexpression of a gene encoding laminin  $\beta$ 1 subunit  
3   relative to the normal control.

1                    78.    (Previously Presented)    The method of Claim 44, further  
2   comprising detecting the overexpression of a gene encoding laminin  $\beta$ 1 subunit  
3   relative to the normal control.